Amended paragraphs with marked revisions

Paragraph at page 1, lines 6-28.

This application is a continuation-in-part of: (1) pending U.S. application Ser. No. 09/449,184, filed November 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/109,924, filed November 24, 1998, and (2) pending U.S. application Ser. No. 09/414,905, filed October 8, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/140,028, filed June 16, 1999 and (3) pending U.S. application Ser. No. 09/449,004, filed November 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/109,923, filed November 24, 1998, and (4) pending U.S. application Ser. No. 09/535,675, filed March 23, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/126,056, filed March 23, 1999, and abandoned U.S. provisional application Ser. No. 60/124,087, filed March 11, 1999 and (5) pending U.S. application Ser. No. 09/449,042, filed November 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/110,127, filed November 27, 1998, and (6) pending U.S. application Ser. No. 09/675,470, filed September 28, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/161,453, filed October 25, 1999, and (7) pending U.S. application Ser. No. 09/586,673, filed June 1, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/145,823, filed July 27, 1999, and (8) pending U.S. application Ser. No. 09/586,672, filed June 1, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/137,745, filed June 3, 1999, and (9) pending U.S. application Ser. No. 09/461,026, filed December 15, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/112,206, filed December 15, 1998, all of which are incorporated herein by reference in their entireties. <u>This application is also a continuation-in-part of pending U.S. provisional application Ser. No. 60/257,071, filed December 18, 2000.</u>

Paragraph at page 12, lines 12-17.

Other embodiments include a method to enhance the expression of one or more cytokines or interleukins that facilitate Th1 immune responses in a subject or to reduce the expression of one or more cytokines or interleukins that facilitate Th2 immune response in a subject comprising administering to the subject an effective amount of [of] a formula 1 compound, whereby the subject's Th1 immune response is enhanced [ot] or the subject's undesired Th2 immune response is reduced.

Paragraph at page 26, line 21 through page 27, line 11.

"Ketal" and "thioketal" mean an organic moiety that is bonded to two adjacent steroid ring atoms in the formula 1 compounds, e.g., ring atoms at the 1-2, 2-3, 3-4, 6-7, 14-15, 15-16 or 16-17 positions. The steroid ring atoms are carbon and the ketal is bonded to each adjacent carbon by an oxygen atom. Thioketals are bonded through one oxygen and one sulfur atom. One, two or more of two adjacent R^1-R^6 and R^{10} may comprise an independently selected ketal or thioketal in any of the formula 1 compounds disclosed herein. The oxygen or [sulfer] sulfur atoms in ketals and thioketals are linked by an optionally substituted alkyl moiety. Typically the alkyl moiety is an optionally substituted C1-C6 alkylene such as $-C(CH_3)_2-$, $-CH(CH_3)-$, $-CH_2-$, $-CH_2-CH_2-$, $-C(C2\text{-}C4\ alkyl)_2-$ or -CH(C2-C4 alkyl)-. Exemplary ketal and thioketals include $-O-C(CH_3)_2-O-$, $-O-C(CH_3)$(heterocycle)-O-, -O-CH(heterocycle)-O-, $-O-C(CH_3)$(aryl)-O-, -O-CH(aryl)-O-, $-S-C(CH_3)_2-O-$, $-O-CH_2-CH_2-O-$, $-O-C(CH_3)_2-CH_2-O-$, $-S-C(CH_3)_2-CH_2-O-$, $-O-C(CH_3)_2-CH_2-S-$ and the like.

Paragraph at page 49, lines 25-30.

Other embodiments include a product produced by the process of contacting BrEA hemihydrate, which may be substantially free of other forms of BrEA, with an excipient suitable for human pharmaceutical use or for veterinary use. The product is useful to make formulations or unit dosage forms that contain the hemihydrate. Exemplary excipients include [onr] one or more of those

disclosed herein, e.g., sucrose, mannitol, starch, carboxymethyl cellulose, magnesium stearate and the like.

Paragraph at page 51, lines 5-25.

Hydrolyzable moieties typically comprise acyl groups, esters, ethers, thioethers, amides, amino acids, peptides, carbonates and/or carbamates. In general, the structure of hydrolyzable moieties is not critical and can vary. In some embodiments, these moieties contain a total of about 4 to about 10 carbon atoms. These hydrolyzable moieties in other embodiments comprise an organic moiety, as described above for ester, that contains 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 13, 14, 15 or 16 carbon atoms and 1, 2, 3, 4, 5, 6, 7 or 8 heteroatoms, e.g., oxygen, nitrogen or sulfur. These hydrolyzable moieties can comprise no groups that are charged in plasma, blood, intracellular cytoplasm or in the gut, or they can comprise 1, 2, 3 or more positive, negative or positive and negative charges under one or more of these conditions. The charges may be fractional depending on the group and the conditions it is under. These hydrolyzable moieties may comprise 1, 2, 3, 4 or more substitutions at a hydrogen atom(s) and/or a carbon atom(s), e.g., -OH, protected hydroxyl, -SH, protected thiol, carboxyl, protected carboxyl, amine, protected amine, -O-, -S-, -CO-, -CS-, alkoxy, alkylthio, alkenyloxy, aryl, -OP(O)(O)-O-, -OS(O)(O)-O- and/or heterocycle. Such substitutions are independently selected. Embodiments of formula 1 compounds include ones wherein one, two, three, four or more of the variable groups that are bonded to the steroid rings, e.g., R^1-R^6 or R^{10}, comprise a moiety that can hydrolyze or [metabolze] <u>metabolize</u> to, e.g., a -H, -OH, =O, -SH, =S, -COOH, -NH_2, -CH_2OH, -CH_2SH, -C(O)-C1-C6 alkyl-OH, -C(O)-C1-C6 alkyl-SH, -C(S)-C1-C6 alkyl-OH, -C(O)-C1-C6 alkyl or -C(O)-NH_2 atom or group.

Paragraph at page 105, lines 6-31.

The subgroups here do not include compounds or genera where two ring heteroatoms are present as described in group 49 and where both R^7 and R^8 are absent ("group 53-52-49-. . . . "), since such groups are mutually incompatible.

This holds for all of the compound groups described herein, i.e., whenever the structures that a first group or subgroup specifies is incompatible with the structure that a second group or subgroup specifies, then the structure that the first group or subgroup [speifies] specifies is not included. However, all other possible compounds and genera are included in such compound groups.

Paragraph at page 120, lines 3-8.

The formula A compounds, including compounds where both R_1 at the 11-position are not hydroxyl, alkoxy or a [moiey] moiety that can hydrolyze to a hydroxyl, are generally suitable for use in the methods and compositions that are disclosed herein, e.g., their use to enhance a subject's Th1 immune responses or to treat inflammation. Methods of administration and dosages for these compounds are essentially as described herein.

Paragraph at page 125, lines 1-11.

Invention embodiments include a method to modulate an immune or cellular response in a subject in need thereof comprising administering to the subject, or delivering to the subject's tissues, an effective amount of a compound of formula 1. Immune and cellular response modulation includes enhancing Th1 immune responses, reducing Th2 immune responses, reducing unwanted or pathological inflammation, enhancing hemopoiesis or modulating the synthesis, level or a biological activity of a biomolecule such as (1) a transcription factor such as a steroid receptor or other factor, (2) a purine such as adenosine, (3) a nucleotide cofactor such as NADPH or (4) another biomolecule as disclosed herein. Typically the subject is in need of such [treament] treatment, e.g., by having a clinical condition disclosed herein or being subject to developing such a condition.

Paragraph at page 125, line 12 through page 126, line 4.

In some embodiments one or more formula 1 compounds or groups of formula 1 compounds may excluded from one or more of the uses disclosed herein. For

example, if the subject is in need of enhanced hemopoiesis, the formula 1 compound optionally excludes 5-androstene-3β-ol-17-one, 5-androstene-3β,17β-diol, 5-androstene-3β,7β,17β-triol or a derivative of any of these three compounds that can convert to these compounds by hydrolysis, or if the subject has or is susceptible to developing a memory impairing neurological disorder or memory impairment condition, the compound is not 5-androstene-3β-ol-7,17-dione or 5-androstene-3β,7-diol-17-one or a derivative of these compounds that can has a group at the 7-position that can convert to -OH or =O by hydrolysis. In other embodiments, formula 1 compound is not 4-pregnene-11β,17α,21-triol-3,20-dione, 17α,21-dihydroxypregn-4-ene-3,11,20-trione, 11β,21-dihydroxy-3,20-dioxopregn-4-en-18-al, 11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione, 17α,21-dihydroxypregna-1,4-diene-3,11, 20-trione, 3β-hydroxypregn-5-ene-20-one, 3β-hydroxyandrost-5-ene-17-one, pregn-4-ene-3,20-dione, 21-hydroxypregn-4-ene-3,20-dione, 9-fluoro-11β,16α,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, 9-fluoro-11β,17α,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, a naturally occurring **[**glucorcorticoid**]** glucocorticoid, a species disclosed herein or a derivative of any of these that can convert to these molecules by hydrolysis or metabolism, e.g., a metabolizable or hydrolyzable ester or ether such as a cyclic ketal, an acetate, a **[**diacetete**]** diacetate, a proprionate, a diproprionate, or an **[**an**]** alkyl, an acyl, e.g., -C(O)-C1-C6 alkyl or another moiety for, e.g., a variable group such as for R^1-R^6 as disclosed herein.

Paragraph at page 138, lines 17-31.

Amines and derivatives of amines, e.g., R^BNH-, R^B-C(O)NH-, R^BOC(O)-NH- or R^BO-C(O)-CHR^B-NH- linked to steroid carbon atoms, are typically prepared by standard methods. For example, amines (NH_2-steroid) are generally prepared using the Hoffmann rearrangement (Br_2, NaOH) from the amide (NH_2-C(O)-steroid) or the Curtius rearrangement (NaN_3) from the acid chloride of the steroid. The R^B substituent can subsequently be introduced by alkylation. Steroid

alcohols can be used as starting materials under standard Mitsunobu conditions (PPh_3, DEAD) to yield N-Boc sulfonamides using N-(t-butoxycarbonyl)-p-toluenesulfonamide. One can selectively remove either protecting group. Treatment with trifluoroacetic acid affords the sulfonamide (R^B-S(O)(O)-NH-steroid). Alternatively, sodium napthalenide deprotects to give the N-Boc compound. Amines (NH_2-steroid) can be converted to amides (R^B-C(O)-NH-steroid) using acyl chlorides (R^B-C(O)-Cl). Treatment with ethyl chloroformate gives the N-carbamate (R^BO-C(O)-NH-steroid). The amine (NH_2-steroid) can be alkylated with an α-bromoester to yield the **[**amio**]** amino acid substituted steroid (R^B-O-C(O)-CHY-NH-steroid).

Paragraph at page 139, line 23 through page 140, line 2.

Scheme 11. Formula 1 compounds that comprise two or three ring heteroatoms are prepared as shown in the following schemes. In the scheme, X is $-CH_2$-, -NH-, -O-, or -S-; R^{40} is -H or –Br; R^{41} is an organic moiety having about 12 carbon atoms or less, typically C1 – C8 optionally substituted alkyl (e.g., methyl, hydroxymethyl, ethyl, propyl, -CH(O), -CH(S)) or C2 – C8 optionally substituted alkenyl having a single double bond (e.g., vinyl) with 1, 2, 3 or more **[**indepenently**]** independently selected substituents (e.g., -OH, -COOH, -O-) and with any substituents that comprise a functional group generally being protected. Preparation of compound 20 from 19 is accomplished using a glycol such as $HOC(CH_3)_2C(CH_3)_2OH$ in acid (H^+) (B.H. Lipshutz et al., *Synth. Commun.* 12: 267, 1982). The use of a bulky protecting group facilitates generation of a double bond at the 5-6 position over the 4-5 position.

Paragraph at page 149, lines 6-10.

Compound 13 and analogs of compound 13 where CH_2, S or NH CH_2 replaces oxygen are **[**preapred**]** prepared as shown in the following reactions. Conditions suitable for conversion of compound 106 to 107 have been described (T. Hamada et al., *Heterocycles* 12: 647, 1979; T. Hamada et al., *J. Am. Chem. Soc.* 108: 140, 1986).

Amended paragraphs

Paragraph at page 1, lines 6-28.

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Other embodiments include a method to enhance the expression of one or more cytokines or interleukins that facilitate Th1 immune responses in a subject or to reduce the expression of one or more cytokines or interleukins that facilitate Th2 immune response in a subject comprising administering to the subject an effective amount of a formula 1 compound, whereby the subject's Th1 immune response is enhanced or the subject's undesired Th2 immune response is reduced.

Paragraph at page 26, line 21 through page 27, line 11.

"Ketal" and "thioketal" mean an organic moiety that is bonded to two adjacent steroid ring atoms in the formula 1 compounds, e.g., ring atoms at the 1-2, 2-3, 3-4, 6-7, 14-15, 15-16 or 16-17 positions. The steroid ring atoms are carbon and the ketal is bonded to each adjacent carbon by an oxygen atom. Thioketals are bonded through one oxygen and one sulfur atom. One, two or more of two adjacent R^1-R^6 and R^{10} may comprise an independently selected ketal or thioketal in any of the formula 1 compounds disclosed herein. The oxygen or sulfur atoms in ketals and thioketals are linked by an optionally substituted alkyl moiety. Typically the alkyl moiety is an optionally substituted C1-C6 alkylene such as $-C(CH_3)_2-$, $-CH(CH_3)-$, $-CH_2-$, $-CH_2-CH_2-$, $-C(C2\text{-}C4\ alkyl)_2-$ or -CH(C2-C4 alkyl)-. Exemplary ketal and thioketals include $-O-C(CH_3)_2-O-$, $-O-C(CH_3)$(heterocycle)-O-, -O-CH(heterocycle)-O-, $-O-C(CH_3)$(aryl)-O-, -O-CH(aryl)-O-, $-S-C(CH_3)_2-O-$, $-O-CH_2-CH_2-O-$, $-O-C(CH_3)_2-CH_2-O-$, $-S-C(CH_3)_2-CH_2-O-$, $-O-C(CH_3)_2-CH_2-S-$ and the like.

Paragraph at page 49, lines 25-30.

Other embodiments include a product produced by the process of contacting BrEA hemihydrate, which may be substantially free of other forms of BrEA, with an excipient suitable for human pharmaceutical use or for veterinary use. The product is useful to make formulations or unit dosage forms that contain the hemihydrate. Exemplary excipients include one or more of those disclosed

herein, e.g., sucrose, mannitol, starch, carboxymethyl cellulose, magnesium stearate and the like.

Paragraph at page 51, lines 5-25.

Hydrolyzable moieties typically comprise acyl groups, esters, ethers, thioethers, amides, amino acids, peptides, carbonates and/or carbamates. In general, the structure of hydrolyzable moieties is not critical and can vary. In some embodiments, these moieties contain a total of about 4 to about 10 carbon atoms. These hydrolyzable moieties in other embodiments comprise an organic moiety, as described above for ester, that contains 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 13, 14, 15 or 16 carbon atoms and 1, 2, 3, 4, 5, 6, 7 or 8 heteroatoms, e.g., oxygen, nitrogen or sulfur. These hydrolyzable moieties can comprise no groups that are charged in plasma, blood, intracellular cytoplasm or in the gut, or they can comprise 1, 2, 3 or more positive, negative or positive and negative charges under one or more of these conditions. The charges may be fractional depending on the group and the conditions it is under. These hydrolyzable moieties may comprise 1, 2, 3, 4 or more substitutions at a hydrogen atom(s) and/or a carbon atom(s), e.g., -OH, protected hydroxyl, -SH, protected thiol, carboxyl, protected carboxyl, amine, protected amine, -O-, -S-, -CO-, -CS-, alkoxy, alkylthio, alkenyloxy, aryl, -OP(O)(O)-O-, -OS(O)(O)-O- and/or heterocycle. Such substitutions are independently selected. Embodiments of formula 1 compounds include ones wherein one, two, three, four or more of the variable groups that are bonded to the steroid rings, e.g., R^1-R^6 or R^{10}, comprise a moiety that can hydrolyze or metabolize to, e.g., a -H, -OH, =O, -SH, =S, -COOH, $-NH_2$, $-CH_2OH$, $-CH_2SH$, -C(O)-C1-C6 alkyl-OH, -C(O)-C1-C6 alkyl-SH, -C(S)-C1-C6 alkyl-OH, -C(O)-C1-C6 alkyl or $-C(O)-NH_2$ atom or group.

Paragraph at page 105, lines 6-31.

The subgroups here do not include compounds or genera where two ring heteroatoms are present as described in group 49 and where both R^7 and R^8 are absent ("group 53-52-49-. . . . "), since such groups are mutually incompatible.

This holds for all of the compound groups described herein, i.e., whenever the structures that a first group or subgroup specifies is incompatible with the structure that a second group or subgroup specifies, then the structure that the first group or subgroup specifies is not included. However, all other possible compounds and genera are included in such compound groups.

Paragraph at page 120, lines 3-8.

The formula A compounds, including compounds where both R_1 at the 11-position are not hydroxyl, alkoxy or a moiety that can hydrolyze to a hydroxyl, are generally suitable for use in the methods and compositions that are disclosed herein, e.g., their use to enhance a subject's Th1 immune responses or to treat inflammation. Methods of administration and dosages for these compounds are essentially as described herein.

Paragraph at page 125, lines 1-11.

Invention embodiments include a method to modulate an immune or cellular response in a subject in need thereof comprising administering to the subject, or delivering to the subject's tissues, an effective amount of a compound of formula 1. Immune and cellular response modulation includes enhancing Th1 immune responses, reducing Th2 immune responses, reducing unwanted or pathological inflammation, enhancing hemopoiesis or modulating the synthesis, level or a biological activity of a biomolecule such as (1) a transcription factor such as a steroid receptor or other factor, (2) a purine such as adenosine, (3) a nucleotide cofactor such as NADPH or (4) another biomolecule as disclosed herein. Typically the subject is in need of such treatment, e.g., by having a clinical condition disclosed herein or being subject to developing such a condition.

Paragraph at page 125, line 12 through page 126, line 4.

In some embodiments one or more formula 1 compounds or groups of formula 1 compounds may excluded from one or more of the uses disclosed herein. For

example, if the subject is in need of enhanced hemopoiesis, the formula 1 compound optionally excludes 5-androstene-3β-ol-17-one, 5-androstene-3β,17β-diol, 5-androstene-3β,7β,17β-triol or a derivative of any of these three compounds that can convert to these compounds by hydrolysis, or if the subject has or is susceptible to developing a memory impairing neurological disorder or memory impairment condition, the compound is not 5-androstene-3β-ol-7,17-dione or 5-androstene-3β,7-diol-17-one or a derivative of these compounds that can has a group at the 7-position that can convert to -OH or =O by hydrolysis. In other embodiments, formula 1 compound is not 4-pregnene-11β,17α,21-triol-3,20-dione, 17α,21-dihydroxypregn-4-ene-3,11,20-trione, 11β,21-dihydroxy-3,20-dioxopregn-4-en-18-al, 11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione, 17α,21-dihydroxypregna-1,4-diene-3,11, 20-trione, 3β-hydroxypregn-5-ene-20-one, 3β-hydroxyandrost-5-ene-17-one, pregn-4-ene-3,20-dione, 21-hydroxypregn-4-ene-3,20-dione, 9-fluoro-11β,16α,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, 9-fluoro-11β,17α,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, a naturally occurring glucocorticoid, a species disclosed herein or a derivative of any of these that can convert to these molecules by hydrolysis or metabolism, e.g., a metabolizable or hydrolyzable ester or ether such as a cyclic ketal, an acetate, a diacetate, a proprionate, a diproprionate, or an alkyl, an acyl, e.g., -C(O)-C1-C6 alkyl or another moiety for, e.g., a variable group such as for R^1-R^6 as disclosed herein.

Paragraph at page 138, lines 17-31.

Amines and derivatives of amines, e.g., R^BNH-, R^B-C(O)NH-, R^BOC(O)-NH- or R^BO-C(O)-CHR^B-NH- linked to steroid carbon atoms, are typically prepared by standard methods. For example, amines (NH_2-steroid) are generally prepared using the Hoffmann rearrangement (Br_2, NaOH) from the amide (NH_2-C(O)-steroid) or the Curtius rearrangement (NaN_3) from the acid chloride of the steroid. The R^B substituent can subsequently be introduced by alkylation. Steroid

alcohols can be used as starting materials under standard Mitsunobu conditions (PPh_3, DEAD) to yield N-Boc sulfonamides using N-(t-butoxycarbonyl)-p-toluenesulfonamide. One can selectively remove either protecting group. Treatment with trifluoroacetic acid affords the sulfonamide (R^B-S(O)(O)-NH-steroid). Alternatively, sodium napthalenide deprotects to give the N-Boc compound. Amines (NH_2-steroid) can be converted to amides (R^B-C(O)-NH-steroid) using acyl chlorides (R^B-C(O)-Cl). Treatment with ethyl chloroformate gives the N-carbamate (R^BO-C(O)-NH-steroid). The amine (NH_2-steroid) can be alkylated with an α-bromoester to yield the amino acid substituted steroid (R^B-O-C(O)-CHY-NH-steroid).

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Scheme 11. Formula 1 compounds that comprise two or three ring heteroatoms are prepared as shown in the following schemes. In the scheme, X is $-CH_2$-, -NH-, -O-, or -S-; R^{40} is -H or –Br; R^{41} is an organic moiety having about 12 carbon atoms or less, typically C1 – C8 optionally substituted alkyl (e.g., methyl, hydroxymethyl, ethyl, propyl, -CH(O), -CH(S)) or C2 – C8 optionally substituted alkenyl having a single double bond (e.g., vinyl) with 1, 2, 3 or more independently selected substituents (e.g., -OH, -COOH, -O-) and with any substituents that comprise a functional group generally being protected. Preparation of compound 20 from 19 is accomplished using a glycol such as $HOC(CH_3)_2C(CH_3)_2OH$ in acid (H^+) (B.H. Lipshutz et al., *Synth. Commun.* 12: 267, 1982). The use of a bulky protecting group facilitates generation of a double bond at the 5-6 position over the 4-5 position.

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